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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/551,263 | NAKASHIMA ET AL. | |
| | Examiner | Art Unit | |
| | OLUWATOSIN OGUNBIYI | 1645 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *16 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-9,11-17 and 21-23* is/are pending in the application.

4a) Of the above claim(s) *23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11-17,21 and 22* is/are rejected.

7)☒ Claim(s) *21* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *9/28/05* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

1. A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 10/16/09 has been entered.

2. Claims 1-9, 11-17 and 21-23 are pending in the application. Claims 1-9, 11-17 and 21-22 are under examination. Claim 23 is withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

***Election by Original Presentation***

3. Newly submitted claim 23 is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: The original claims were drawn to a product i.e. a modified Staphylococcal enterotoxin B as set forth in the claims set of 9/28/05. Amended claims of 6/12/08 and 10/16/09 were also drawn to a modified Staphylococcal enterotoxin B as set forth in the amended claims submitted on 6/12/08 and 10/16/09 respectively. The examined product and the method now claimed in claim 23 are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially

different process of using that product. See MPEP § 806.05(h). In the instant case the product as claimed can be used in a method of treating lupus.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 23 is withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

***Sequence Requirements***

4. Applicants have stated that the Application is in sequence compliance because the amino acid sequence of the Staphylococcal enterotoxin B (SEB) referenced in the claim set of 6/12/08 is SEQ ID NO: 1 and is submitted within a sequence listing made of record. Therefore, the application has complied with the requirements of 37 C.F.R. § 1.821-1.825.

***Rejections Withdrawn***

5. The rejection of claims 1, 2, 3, 8, 9-13 and 18-20 provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1,4,6-9 of copending Application No.10/570,499 is withdrawn in view of the abandonment of copending Application No.10/570,499.

6. The rejection of claims 9-11 and 18-21 under 35 U.S.C. 112, first paragraph because the specification (scope of enablement) is withdrawn in view of the cancellation of claim 10 and 18-20 and favour of a new rejection set forth below in paragraph number 19.

7. The rejection of claims 5-7 and 15-17 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the recitation in the claims the amino acid sequence of SEB as shown in SEQ ID NO: 1.

8. The rejection of claims 3, 8, 10, 12-13 and 18-20 under 35 U.S.C. 102(b) as being clearly anticipated by Sasaki et al. EP 1055429 A1 published 11/29/2000 is withdrawn in view of the cancellation of claim 10 and claims 18-20 and because Sasaki et al does not disclose that an amino acid substitution was introduced at an epitope recognition site of the anti-SEB antibody and Sasaki et al does not disclose Asn at 23 position in the amino acid sequence of SEB as shown SEQ ID NO: 1 is substituted with Tyr. Sasaki et al does not disclose the amino acid sequence of SEB as shown SEQ ID NO: 1.

9. The rejection of claims 4, 10 and 11 under 35 U.S.C. 102(b) as being clearly anticipated by Nishi et al (The Journal of Immunology, 1997, 1558:247-254) is withdrawn in view of the cancellation of claim 10, the amendment to claim 11 and the amendment to claim 4 which now sets forth the sequence of SEB as shown in SEQ ID NO: 1. Nishi et al does not disclose SEQ ID NO: 1.

10. The rejection of claims 3, 8, 10, 12-13 and 18-20 under 35 U.S.C. 102(b) as being clearly anticipated by Kappler et al. WO93/14634 Aug. 5 1993 is withdrawn in view of the cancellation of claim 10 and claims 18-20 and because Kappler et al does not disclose Asn at 23 position in the amino acid sequence of SEB as shown SEQ ID NO: 1 is substituted with Tyr. Kappler et al does not disclose the amino acid sequence of SEB as shown in SEQ ID NO: 1.

11. The rejection of claims 1-21 under 35 U.S.C. 103(a) as being obvious over Nishi et al. The Journal of Immunology, 1997, 1558:247-254 in view of Sasaki et al EP 1055429 A1 published 11/29/2000 and Kappler et al. WO93/14634 Aug. 5 1993 is withdrawn in view of the amendment to claim 11, in view of the cancellation of claims 10 and 18-20 and because as to claims 4-8, 12-17 and 21, neither Nishi or Sasaki or Kappler discloses the amino acid sequence of SEB as shown in SEQ ID NO: 1.

***Rejections Maintained***

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. The rejection of claim 21 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained.

Claim 21 is indefinite and vague because it recites "…introducing in the amino acid sequence of SEB as shown in SEQ ID NO: 1 an amino acid substitution from Lys at the 226-position to Lys at the 229-position of Leu Phe Ala Ala, Ala Thr Thr Gln or Lys Arg Ile Ile…". It is not clear as claimed whether the substitution at position 226 to 229 is any combination of each of the amino acids listed. It is suggested that applicants clarify the claim to indicate that as a result of the substitution at positions 226 to 229 of the amino acid sequence of SEB as shown in SEQ ID NO: 1, the amino acid residues at position 226-229 are substituted with Leu, Phe, Ala,

Ala, respectively or substituted with Ala Thr Thr Gln, respectively or substituted with Lys Arg Ile Ile, respectively, if this is what Applicants mean and is supported by the specification.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. The rejection of claims 1-2, 9, 11 and newly applied to new claim 22 under 35 U.S.C. 102(b) as being clearly anticipated by Sasaki et al. EP 1055429 A1 published 11/29/2000 is maintained.

Claim 1 and dependent claims are drawn to a modified Staphylococcal enterotoxin B (SEB) having a reduced reactivity with a neutralizing antibody to SEB (anti-SEB antibody) and being soluble in water, wherein the reactivity with the anti-SEB antibody was reduced by introducing arbitrary amino acid substitution in the amino acid sequence of SEB wherein the amino acid substitution was introduced at an epitope recognition site of the anti-SEB antibody in the amino acid sequence of SEB; wherein Asn at 23-position in the amino acid sequence of SEB as shown in SEQ ID NO: 1 is substituted with Tyr.

Claim 22 and dependent claims are drawn to a remedy comprising the modified SEB mutant N23Y or 47c7 or 4c1 wherein said mutants have reduced binding to an anti-SEB

antibody and wherein said mutants produce inhibitory cytokines at higher levels compared to the production of inflammatory cytokines as compared to wild type SEB for treatment of rheumatoid arthritis.

Sasaki et al discloses a modified Staphylococcal enterotoxin B (SEB). Sasaki discloses said modified enterotoxin with arbitrary amino acid substitutions at epitope recognition site (p.3 paragraph 12 -14, p. 4 paragraphs 17, 18, 19, 23, p. 8 table 3). Sasaki discloses a modified SEB wherein Asn at 23-position in the amino acid sequence of SEB is substituted with Tyr (p.3 paragraph 12, p. 8 table 3). Since Sasaki discloses a modified SEB as instantly claimed, for example, Asn at 23-position in the amino acid sequence of SEB is substituted with Tyr i.e. a **N23Y** SEB mutant. Sasaki discloses that said modified enterotoxin is used as a remedy for immunopathy (e.g. rheumatoid arthritis) having reduced immunological response to SEB and inhibitory activity on T cell activation (see abstract and claims 1-13 p. 12) and is in a form for oral administration (claims 1-13). Since Sasaki et al names the modified SEB such as N23Y and others, said modified SEB mutant will have the inherent property of having a reduced reactivity with a neutralizing antibody to SEB, have reduced binding to an anti-SEB antibody, be soluble in water and produce inhibitory cytokines at higher levels compared to the production of inflammatory cytokines as compared to wild type SEB for treatment of rheumatoid arthritis.

"If the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present". In re Spada 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01. In the instant case, Sasaki et al discloses a modified SEB comprising amino acid substitution in the amino acid sequence of SEB and therefore meets the structural limitation of claims 1-2, 9, 11 and 22.

As to the recitation of "A treatment composition" or "remedy" in claim 9 and 11 respectively, if the body of a claim fully and intrinsically sets forth all of the limitations of the claimed invention, and the preamble merely states, for example, the purpose or intended use of the invention, rather than any distinct definition of any of the claimed invention's limitations, then the preamble is not considered a limitation and is of no significance to claim construction. *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305, 51 USPQ2d 1161, 1165 (Fed. Cir. 1999). See also *Rowe v. Dror*, 112 F.3d 473, 478, 42 USPQ2d 1550, 1553 (Fed. Cir. 1997) ("where a patentee defines a structurally complete invention in the claim body and uses the preamble only to state a purpose or intended use for the invention, the preamble is not a claim limitation"). The recitations of "A treatment composition" or "remedy" do not result in any structural difference of the claimed product. Similarly, the recitation of "for treatment of rheumatoid arthritis" does not result in any structural differences in the claimed product.

Applicants arguments:

> With reference to paragraph [0012] of Sasaki, it is seen that Sasaki gives too many alternatives for substitution at the 23 position for there to be a valid rejection based on §102. Sasaki does not put the reader of Sasaki in possession of the presently claimed subject matter.
>
> For a reference to be properly anticipatory under §102, the reference must disclose each and every element of the claimed invention, *Eli Lilly and Co. v. Zenith Goldline Pharmso, Inc.,* 81 USPQ2d 1324, 1328 (Fed. Cir. 2006), and those elements must be "arranged or combined in the same way as in the claim," *Net MoneyIN Inc. v. VeriSign Inc.,* 88 USPQ2d 1751, 1759 (FedCir. 2008), quoting from Finisar Corp. v. DirecTV Group Inc., 86 USPQ2d 1609, 1618 (Fed. Cir. 2008). Applicants do not see that Sasaki meets the test for being properly anticipatory under §102 as required by the aforementioned case law.

> Moreover, Applicants do not understand the bottom paragraph on page 5 of the Office Action. Applicants do not understand what Nishi has to do with a rejection based on Sasaki, and does not understand what the reference to Nishi has to do with what is commensurate in scope with Applicants' claims.

Response:

All of Applicants arguments have been carefully considered but is not found persuasive. Applicants focus on paragraph 12 of Sasaki et al but in the rejection above, Applicants were directed to different relevant portion of Sasaki et al that disclose and name specific modified SEB and also name particular amino acid substitutions including the particular amino acids at particular positions of the SEB amino acid sequence. For instance, in paragraph 17, names a substitution of asparagine (Asn) at position 23 and Sasaki et al names different substitutions such as N23D, N23K, N23Y, N23I. Sasaki et al further lists in paragraph 17 other modifications of SEB including the following substitutions I41T, L45V etc. Sasaki et al teaches how the SEB mutants were made (paragraphs 44-52 particularly paragraphs 50-52) and table 3 specifically names sites to be modified and names particular substitutions. Since Sasaki et al names the modified SEB such as N23Y and others said modified SEB will the inherent property of having a reduced reactivity with a neutralizing antibody to SEB, have reduced binding to an anti-SEB antibody, be soluble in water and produce inhibitory cytokines at higher levels compared to the production of inflammatory cytokines as compared to wild type SEB for treatment of rheumatoid arthritis.

Applicants argument that Sasaki et al does not put the reader of Sasaki in possession of the claimed invention is not persuasive. When a reference discloses a class of compounds, i.e., a genus, a person of ordinary skill in the art should be able to "at once envisage each member of

the th[e] … class" for the individual compounds, i.e., species, to be enabled. *In re Petering*, 301 F. 2d 676, 681 (C.C.P.A. 1962). Furthermore, when the species is clearly named, the species claim is anticipated no matter how many other species are additionally named. *Ex parte A*, 17 USPQ2d 1716 (Bd. Pat. App. & Inter. 1990). In the instant case, Sasaki et al clearly names different types of modified SEBs including a N23Y SEB mutant and thus anticipates the instant invention.

Applicants state that they do not understand the bottom paragraph on page 5 of the previous Office Action. Applicants do not understand what Nishi has to do with a rejection based on Sasaki, and does not understand what the reference to Nishi has to do with what is commensurate in scope with Applicants' claims. In response, Applicants are reminded that in the previous response filed 6/12/08 p. 10 starting from the second to the last paragraph to the first paragraph of p. 11, Applicants in response to the rejection under 35 U.S.C. 102(b) as anticipated by Sasaki stated that " However, it is not seen that Sasaki discloses the claimed subject matter, e.g. a modified SEB which inherently avoids the problem mentioned at the bottom of p. 6 of Applicants' specification". Since Applicants did not point to the problem on p. 6 by line number, it was assumed that Applicants were referring to lines 20-25 in which Applicants site Nishi et al in which a modified SEB lacking an epitope at the C-terminal was made and which Applicants stated could not be expressed in soluble form.

Therefore, because Applicants had directed the Office to the "problem at the bottom of p. 6 of the specification", the response by the Office addressed Nishi et al as the "problem at the bottom of p. 6 of the specification", is drawn to Nishi et al in which a modified SEB lacking an

epitope at the C-terminal was made and which Applicants stated could not be expressed in soluble form.

14. The rejection of claims 1-3 and 9 under 35 U.S.C. 102(b) as being clearly anticipated by Nishi et al (The Journal of Immunology, 1997, 1558:247-254) is maintained.

The claims are drawn to a modified Staphylococcal enterotoxin B (SEB) having a reduced reactivity with a neutralizing antibody to SEB (anti-SEB antibody) and being soluble in water, wherein the reactivity with the anti-SEB antibody was reduced by introducing arbitrary amino acid substitution in the amino acid sequence of SEB wherein the amino acid substitution was introduced at an epitope recognition site of the anti-SEB antibody in the amino acid sequence of SEB; wherein the amino acid substitution was introduced within a region from Lys at 226-position to Lys at 229-position in the amino acid sequence of SEB as shown in SEQ ID NO: 1.

Nishi et al discloses a modified Staphylococcal enterotoxin B (SEB). Nishi discloses said modified enterotoxin with arbitrary amino acid substitutions at an epitope recognition site (p.250 column 1 last bridging paragraph to column 2). Nishi teaches a modified SEB wherein the amino acid substitution was introduced within a region from Lys at 226-position to Lys at 229-position in the amino acid sequence of SEB (p.250 column 1 last bridging paragraph to column 2). Nishi teaches that said modified enterotoxin has reduced reactivity with an IgG antibody (p. 252 fig. 6 and column 2 last two paragraphs to p. 253 first paragraph). Said modified SEB of Nishi et al inherently possess reduced reactivity with a neutralizing anti-SEB antibody and will be soluble in water and possesses reduced immunological response to SEB and an inhibitory activity to T

cell activation. Nishi teaches said modified SEB is purified and dialyzed against PBS (phosphate buffered saline). Thus, said modified SEB is an active ingredient in said PBS which is a pharmaceutically acceptable carrier. As to the recitation of "A treatment composition" in claim 9, if the body of a claim fully and intrinsically sets forth all of the limitations of the claimed invention, and the preamble merely states, for example, the purpose or intended use of the invention, rather than any distinct definition of any of the claimed invention's limitations, then the preamble is not considered a limitation and is of no significance to claim construction. *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305, 51 USPQ2d 1161, 1165 (Fed. Cir. 1999). See also *Rowe v. Dror*, 112 F.3d 473, 478, 42 USPQ2d 1550, 1553 (Fed. Cir. 1997) ("where a patentee defines a structurally complete invention in the claim body and uses the preamble only to state a purpose or intended use for the invention, the preamble is not a claim limitation"). The recitation "A treatment composition" or "remedy" do not result in structural difference of the claimed product.

Applicants arguments:

> As pointed out at the bottom of page 6 of the Applicants' specification, Nishi suggests that a major epitope recognized by an anti-SEB antibody in human serum is located at the C-terminal of SEB, and an antibody against such C-terminal region is a neutralizing antibody to SEB. The solution proposed by Nishi could only be expressed in an insoluble form, and therefore does not conform with what is inherently present in Applicants' claims. The Examiner says that the argument is not commensurate in scope with Applicants' claims, but Applicants respectfully maintain that their claims inherently define over Nishi.

Response:

Applicants arguments are carefully considered but are not found persuasive. The instant claims now recite the limitation " being soluble in water". Applicants at the bottom of p. 6 teach that the prepared modified SEB of Nishi et al could only be expressed in a soluble form. There is no evidence in Nishi et al that the modified SEB is insoluble in water. The structure implied by the process steps should be considered when assessing the patentability of product-by-process claims over the prior art, especially where the product can only be defined by the process steps by which the product is made, or where the manufacturing process steps would be expected to impart distinctive structural characteristics to the final product. See, e.g., *In re Garnero*, 412 F.2d 276, 279, 162 USPQ 221, 223 (CCPA 1979). The instant claims have broad and generic structural limitations which are meet by Nishi et al. The SEB of Nishi et al is modified and has amino acid substitutions introduced at an epitope recognition site. Claims 1-3 and 9 do not sufficiently structurally distinguish from Nishi et al. Since, the modified SEB of Nishi et al meets the generic structural limitations of the instantly claimed modified SEB, then the modified SEB of Nishi et al would inherently have the same properties. Therefore, "if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present". In re Spada 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01. As a practical matter, the Patent Office is not equipped to manufacture products by the myriad of processes put before it and then obtain prior art products and make physical comparisons therewith." *In re Brown*, 459 F.2d 531, 535, 173 USPQ 685, 688 (CCPA 1972).

15. The rejection of claims 1-2, 9, 11 and newly applied to claim 22 under 35 U.S.C. 102(b) as being clearly anticipated by Kappler et al. WO93/14634 Aug. 5 1993 is maintained.

Claim 1 and dependent claims are drawn to a modified Staphylococcal enterotoxin B (SEB) having a reduced reactivity with a neutralizing antibody to SEB (anti-SEB antibody) and being soluble in water, wherein the reactivity with the anti-SEB antibody was reduced by introducing arbitrary amino acid substitution in the amino acid sequence of SEB wherein the amino acid substitution was introduced at an epitope recognition site of the anti-SEB antibody in the amino acid sequence of SEB; wherein Asn at 23-position in the amino acid sequence of SEB as shown in SEQ ID NO: 1 is substituted with Tyr.

Claim 22 and dependent claims are drawn to a remedy comprising the modified SEB mutant N23Y or 47c7 or 4c1 wherein said mutants have reduced binding to an anti-SEB antibody and wherein said mutants produce inhibitory cytokines at higher levels compared to the production of inflammatory cytokines as compared to wild type SEB for treatment of rheumatoid arthritis.

Kappler et al teaches a modified Staphylococcal enterotoxin B (SEB) (p. 38). Kappler teaches said modified enterotoxin with arbitrary amino acid substitutions in the amino acid sequence of SEB (p.38 table II). Kappler teaches a modified SEB wherein Asn at 23-position in the amino acid sequence of SEB is substituted with Tyr i.e. an N23Y mutant(p.38 table II and III see BC-66 mutant). Since Kappler et al discloses a modified SEB as instantly claimed, for example, Asn at 23-position in the amino acid sequence of SEB is substituted with Tyr, said modified SEB of Kappler et al inherently possess reduced reactivity with a neutralizing anti-SEB

antibody, soluble in water, possesses reduced immunological response to SEB and an inhibitory activity to T cell activation, has reduced binding to an anti-SEB antibody and produce inhibitory cytokines at higher levels compared to the production of inflammatory cytokines as compared to wild type SEB for treatment of rheumatoid arthritis. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01.

Kappler et al teaches said modified SEB in a balanced salt solution (BSS) thus said modified SEB is in a form for oral administration and thus in a form adapted for immunopathy.

As to the recitation of "A treatment composition" or "remedy" in claim 9 and 11 respectively, if the body of a claim fully and intrinsically sets forth all of the limitations of the claimed invention, and the preamble merely states, for example, the purpose or intended use of the invention, rather than any distinct definition of any of the claimed invention's limitations, then the preamble is not considered a limitation and is of no significance to claim construction. *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305, 51 USPQ2d 1161, 1165 (Fed. Cir. 1999). See also *Rowe v. Dror*, 112 F.3d 473, 478, 42 USPQ2d 1550, 1553 (Fed. Cir. 1997) ("where a patentee defines a structurally complete invention in the claim body and uses the preamble only to state a purpose or intended use for the invention, the preamble is not a claim limitation"). The limitations "A treatment composition" or "remedy" do not result in structural difference of the claimed product. Similarly, the recitation of "for treatment of rheumatoid arthritis" does not result in any structural differences in the claimed product.

Applicants arguments:

Applicants do not agree that the recitation "adapted for immunopathy" is a statement of intended use, but instead Applicants respectfully submit that it defines a characteristic of the claimed subject matter and therefore defines in part what is being claimed rather than an intended use. Withdrawal of the rejection is in order and is respectfully requested.

Response:

Applicants' arguments are carefully considered but are not persuasive.

Applicants only address the limitation in claim 9 which recites "adapted for immunopathy". As stated in the rejection above, Kappler et al teaches said modified SEB in a balanced salt solution (BSS) thus said modified SEB is in a form for oral administration and thus in a form adapted for immunopathy. Furthermore, "in a form adapted for immunopathy" is intended use and is interpreted that the modified SEB of claim 9 is in a form used for immunopathy. Kappler et al teaches said modified SEB in a balanced salt solution (BSS) thus said modified SEB is in a form for oral administration and thus in a form adapted for immunopathy. Thus, claim 9 is anticipated by Kappler et al. Applicants did not address the rejections over claims 1-2 and 11, therefore the rejection of these claims are maintained.

***New Objections/Rejections Based on Amendment***

***Claim Objections***

16. Claim 21 objected to because of the following informalities: In line 4, please italicize "*E. coli*". Appropriate correction is required.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

17. Claims 1-9 and 12-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection**.

Claim 1 and dependent claims are drawn to a modified Staphylococcal enterotoxin B (SEB) having a reduced reactivity with a neutralizing antibody to SEB (anti-SEB antibody) and being soluble in water.

The limitation "being soluble in water" is drawn to new matter. There is no disclosure in the specification of a modified Staphylococcal enterotoxin B (SEB) having a reduced reactivity with a neutralizing antibody to SEB and being soluble in water. The specification on p. 8 lines 6-10 states "…the present inventors could successfully prepare a modified SEB that has a reduced binding to the anti-SEB neutralizing antibody and is capable of being expressed in a soluble form in *E. coli*…". "Expressed in a soluble form in *E. coli*" is not equivalent to "being soluble in water". Applicants may point to the specification by page number and line number for where support exists for the limitation in claim 1, "being soluble in water".

18. Claims 1-3 and 9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the

relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a written description rejection**.

Claim 1 is drawn to a modified Staphylococcal enterotoxin B (SEB) having a reduced reactivity with a neutralizing antibody to SEB (anti-SEB antibody) and being soluble in water.

Claim 2 the modified SEB of claim 1 wherein the reactivity with the anti-SEB antibody was reduced by introducing arbitrary amino acid substitution in the amino acid sequence of SEB.

Claim 3 the modified SEB of claim 2 wherein the amino acid substitution was introduced at an epitope recognition site of the anti-SEB antibody in the amino acid sequence of SEB.

Claim 9 is drawn to a treatment composition comprising as an active ingredient the modified SEB as set forth in claim 1, wherein said treatment composition provides a reduced immunological response to SEB and an inhibitory activity to T cell activation, said treatment composition being in a form adapted for immunopathy.

Claim 1 and claim 9 is drawn to a large and variant genus of modified SEB proteins comprising numerous structurally distinct species as a result of deletion(s), insertion(s), substitution(s) or combinations thereof in any SEB amino acid sequence. The specification does not define “modified” and thus "modified” includes deletion(s), insertion(s), substitution(s) or combinations thereof. The claims require that the genus have a reduced reactivity with a neutralizing antibody to SEB (anti-SEB antibody) and being soluble in water (claim 1) and additionally provides a reduced immunological response to SEB and an inhibitory activity to T cell activation (claim 9).

Claim 2 is drawn to a large and variant genus of modified SEB proteins comprising numerous structurally distinct species as a result of arbitrary amino acid substitution along anywhere in any SEB amino acid sequence.

Claim 3 is also drawn to a large and variant genus of modified SEB comprising numerous structurally distinct species as a result of arbitrary amino acid substitution anywhere in at an epitope recognition site of the anti-SEB antibody in any SEB amino acid sequence.

Actual Reduction to practice: The specification teaches a N23Y mutant substitution of asparagine with tyrosine at position 23 of the amino acid sequence of SEB which has reduced reactivity to an anti-SEB antibody. The specification reduces to practice SEB mutants with reduced reactivity which comprise the N23Y substitution in addition to the substitutions introduced at an epitope recognition site i.e. position 226 to position 229 of the amino acid sequence of SEB set forth in SEQ ID NO: 1. See p. 19 lines 8-14 and table 23 table 1. The specification teaches that the modified SEB reduced to practice based on the amino acid sequence of native SEB (SEQ ID NO: 1) are expressed in soluble form in *E. coli.* The specification that said modified SEB reduced to practice produced more inhibitory cytokines and induced inflammatory cytokines at a relatively lower level and it was supposed that the modified SEB had an activity to shift T cell populations from Th1 or Th2. The specification does not reduce to practice any modified SEB with inhibitory activity to T cell activation but instead teaches that the modified SEB comprising amino acid substitution at position 23 i.e. N23Y and/or other substitutions at position 226 to 229 of SEQ ID NO: 1 shifted T cell populations from Th1 or Th2 resulting in production of more inhibitory cytokines.

Sufficient Relevant Identifying Characteristics: The specification disclose the amino acid sequence of a SEB i.e. SEQ ID NO: 1 and teaches amino acid substitution at position 226 to 229 of SEQ ID NO: 1 which is the epitope recognition site. See p. 10 lines 14-24. The specification does not disclose any other SEB amino acid sequence and the cognate epitope recognition site. The specification does not disclose identifying characteristics i.e. partial, complete, physical or chemical or a correlation between function and structure of members of the genus of modified SEB with inhibitory activity to T cell activation. The specification does not disclose identifying characteristics i.e. partial, complete, physical or chemical or a correlation between function and structure of other members of the genus of modified SEB (with insertions, deletions or other substitutions (apart from those disclosed) or combinations thereof anywhere in the amino acid sequence of any SEB amino acid sequence with reduced reactivity with a neutralizing antibody to SEB and being soluble in water and which provides a reduced immunological response to SEB.

Method of Making the invention: The only amino acid sequence of a SEB disclosed is SEQ ID NO: 1 and teaches that the epitope recognition site is position 226-229 of SED ID NO: 1. The specification teaches a method of making modified SEB comprising substitutions N23Y and substitutions in amino acid position 226-229 using a template plasmid pTrc99A/N23Y in which one of the known modified SEBs N23Y was incorporated into pTrc99A and PCR was performed to introduce random mutations at position 226-229. See p. 19 lines 7-25.

Predictability in the art: As of the time of filing there was no art recognized correlation between insertion(s), deletion(s) or substitution(s) or combinations thereof in the amino acid sequence of SEB as shown in SEQ ID NO: 1 and its characteristic as being soluble in water and

reduced reactivity with neutralizing antibody to SEB as required by claims 1-3 or characteristic as being soluble in water and reduced reactivity with neutralizing antibody to SEB and reduced immunological response to SEB and inhibitory activity to T cell activation as required by claim 9.

While general knowledge in the art may have allowed one of skill in the art to identify other modified SEBs (apart from the ones reduced to practice) expected to have the same or similar tertiary structure of the disclosed modified SEBs, there is no general knowledge in the art about solubility of SEB in water to suggest that general similarity of structure or that arbitrary amino acid substitution or any type of modification (insertion(s), deletion(s), substitution(s) or combinations thereof) any where in the any amino acid sequence of SEB confers being soluble in water and reduced reactivity with neutralizing antibody to SEB as required by claims 1-3 or characteristic as being soluble in water and reduced reactivity with neutralizing antibody to SEB and reduced immunological response to SEB and inhibitory activity to T cell activation as required by claim 9.

*Vas-Cath, Inc. v. Mahurkar,* 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention". "Without a correlation between structure and function, the claim does little more than define the claimed invention by function. That is not sufficient to satisfy the written description requirement". See *Eli Lilly,* 119 F.3d at 1568, 43 USPQ2d at 1406. Further, possession may not be shown by merely described how to obtain possession of members of the claimed genus or how to identify their common structural features. See University of Rochester, 358 F.3d at 927, 69USPQ2d at 1895.

Applicant is reminded that *Vas-Cath, Inc. v. Mahurkar* makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115). Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001 and revision of the Written Description Training materials, Revision 1 March, 2008 http://www.USPTO.gov/web/menu/written.pdf.

In conclusion, Applicants as of the time of filing were only in possession of a modified Staphylococcal enterotoxin B (SEB) having a reduced reactivity with a neutralizing antibody to SEB (anti-SEB antibody) and being expressed in soluble form in *E.coli* wherein amino acid substitution is introduced at position 23 of SEQ ID NO: 1 and positions 226 to 229 of SEQ ID NO: 1, wherein the modified SEB provides a reduced immunological response to SEB and produces inhibitory cytokines at higher levels compared to the production of inflammatory cytokines but were not in full possession of the genus of modified SEB proteins having a reduced reactivity with a neutralizing antibody to SEB (anti-SEB antibody) and being soluble in water and not in full possession of the genus of modified SEB proteins having a reduced reactivity with a neutralizing antibody to SEB (anti-SEB antibody) and being soluble in water reduced and having a reduced immunological response to SEB and an inhibitory activity to T cell activation,

19. Claims 1-9, 11-17 and 21 are rejected under 35 U.S.C. 112, first paragraph because the specification, while being enabling for a remedy used for treating rheumatoid arthritis comprising the modified SEB mutant N23Y wherein Asn at 23 position in the amino acid sequence of SEB as shown in SEQ ID NO: 1 is substituted with Tyr or modified SEB

mutant 47-C-7 wherein the amino acid sequence of SEB at position 226-229 as shown in SEQ ID NO: 1 is Ala Thr Thr Gln or modified SEB mutant 47-C-1 wherein the amino acid sequence of SEB at position 226-229 as shown in SEQ ID NO: 1 is Lys Arg Ile Ile, does not reasonably provide enablement for any other SEB mutants including modified SEB mutant 42-C-2 wherein the amino acid sequence of SEB at position 226-229 as shown in SEQ ID NO: 1 is Lys Phe Ala Ala. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The facts that should be considered in determining whether a specification is enabling or if it would require an undue amount of experimentation to practice the invention include 1) the quantity of experimentation necessary to make or use the invention based on the content of the disclosure, (2) the amount of direction or guidance presented, 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breadth of the claims. *In re Wands*, 858 F.2d 731, 735 (Fed. Cir.1988). The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. While the analysis and conclusion of a lack of enablement are based on these factors discussed in MPEP § 2164.01(a) and the evidence as a whole, the factors that weigh more in making the instant enablement rejection were discussed in the previous action and as set forth below.

**Nature of the invention and breadth of the claims**

The nature of the instant invention is the use of a modified Staphylococcus Enterotoxin B (SEB). The specification teaches that they are used for prophylactics or remedies for immunopathy such as rheumatoid arthritis, allergic disease etc. See p. 1 of the specification. The instant specification does not define immunopathy. The dictionary definition of immunopathy includes any abnormal immune response i.e. a deficient or absent immune response (e.g. combined immunodeficiency), excess production of gamma globulins, over-reaction to extrinsic antigens as in immediate and delayed type hypersensitivity and over-reaction to intrinsic antigens e.g. autoimmune diseases such as lupus erythematosus and thyroiditis (Definition of Immunopathy cited previously:

http://medical-dictionary.thefreedictionary.com/immunopathy) The specification also states that immunopathy can be rheumatoid arthritis or allergic diseases (see p. 1 lines 11-12 of specification). Prophylaxis or prevention as used here means to prevent the occurrence of all these immunopathy or rheumatoid arthritis or allergic disease in a subject who has never had immunopathy or rheumatoid arthritis or allergic disease. The specification does not provide any special definition for prophylaxis.

The modified SEB can comprise any modification including including those specifically recited in the claims e.g. substitutions at position 23 of the amino acid of SEB as shown in SEQ ID NO: 1 or substitutions at positions 226-229 of the amino acid sequence of SEB as shown in SEQ ID NO: 1. The specification does not define “modified” and thus "modified" includes deletion(s), insertion(s), substitution(s) or combinations thereof.

Guidance in the specification and the presence or absence of working examples

The teachings of the specification are limited to inhibition of symptoms of arthritis by administering a modified SEB N23Y mutant or modified SEB with the N23Y mutation in combination with the mutations at position 226-229. See construction and isolation of mutants on p. 19- 22, p. 23 table 1.. Briefly, mice were given type II collagen twice to induce arthritis then said mice were administered the modified SEB. See p. 26-27 and figure 1. The specification on p. 27 and figure 6 teaches that the N23Y, the 47-C-7 and 4-C-1 mutants reduced symptoms of arthritis while the 42-C-2 mutant had no inhibitory activity. The modified SEB with the N23Y mutation in combination with the 226 to 229 mutation (Leu Phe Ala Ala) i.e. mutant 42-C-2 failed to reduce symptoms due to arthritis. This example shows the unpredictability of any modified SEB in treating rheumatoid arthritis or any immunopathy. In addition, this example showed that arthritis symptoms were treated in mice *having* arthritis with particular modified SEB. Example 4 is completely different from prevention or prophylaxis of arthritis. The specification is devoid of an example whereby mice *not* having arthritis is given the instantly modified SEB or other modified SEB and monitored over time to see if they develop arthritis or any other immunopathy (as set forth above).

The specification teaches that the disclosed modified SEBs had proliferation activity on PBMCs (p. 23-24) and induced inhibitory cytokines at higher levels and induced inflammatory cytokines at lower levels relative to wild type SEB (p. 25). The specification does not correlate the cytokine inducing pattern of the modified SEBs disclosed in the specification with prevention or prophylaxis of any immunopathy including rheumatoid arthritis. The specification does not provide guidance as to which particular modified SEB prevents immunopathy or rheumatoid

arthritis or allergic diseases. The example in the specification clearly shows that not all modified SEBs can even treat ongoing arthritis in the mice.

The state of the prior art

The state of the prior art as at the time of filing teaches that "until we know the exact cause of rheumatoid arthritis and can therefore direct therapy at the inciting cause or at the earliest steps in the patho-physiologic sequence, the molecules mediating joint damage are the logical targets of anti-rheumatoid arthritis therapy" (Smith et al. Ann Intern Med 2002; 136:908-922 p. 916 right column last paragraph to p. 917, cited previously)). Thus, the art teaches that there is anti-rheumatoid arthritis therapy directed at molecules mediating joint damage i.e. in humans having rheumatoid arthritis. The prior art stated that the exact cause of rheumatoid arthritis is unknown. Rheumatoid arthritis is an autoimmune disease its etiology remains elusive although it appears that genetic, infectious, environmental and hormonal factors are involved (Smith et al). Thus, prevention of rheumatoid arthritis in humans which such complex underlying factors is unpredictable and the specification does not correlate the cytokine inducing activities of the instantly disclosed modified SEBs with prevention i.e. prophylaxis of rheumatoid arthritis in any animal model.

Furthermore, claim 9 recites that the modified SEB provide an inhibitory activity to T cell activation. However, this is not the case because as evidenced by the specification, the disclosed modified SEBs was able to activate PBMCs and induce the production of cytokines. Production of cytokines (inhibitory or inflammatory) entails the activation of a T cell. Thus, the modified SEBs does not provide for an inhibitory activity to T cell activation but rather they induce more of inhibitory cytokines as compared to inflammatory cytokines.

As to the use of any modified SEB to treat any immunopathy or rheumatoid arthritis, superantigens are secreted proteins that exhibit highly potent lymphocyte transforming mitogenic activity directed towards T cells and they cause massive immune responses that are non-specific and detrimental (Llewelyn et al. 2002. The Lancet Infectious Diseases 2: 156-162, cited previously) and this T cell activating mechanism has been harnessed for the treatment or killing of tumor cells (Forsberg et al WO 03/002143 A1 Jan. 9, 2003, cited previously). Forsberg et al teaches modified Staphylococcal enterotoxins having superantigen activity used to make conjugates to treat tumors). The specification does not teach which other modified SEBs will not induce massive immune responses which can exacerbate certain immunopathy e.g. rheumatoid arthritis instead of treating the condition.

In view of the nature of the invention, the breadth of the claims, the unpredictability of using any modified SEB to treat or prevent immunopathy including rheumatoid arthritis, the state of the prior art, the guidance in the specification and the lack of working example of modified SEB having inhibitory activity to T cell, the specification is enabling for a remedy comprising the modified SEB mutant N23Y wherein Asn at 23 position in the amino acid sequence of SEB as shown in SEQ ID NO: 1 is substituted with Tyr or modified SEB mutant 47-C-7 wherein the amino acid sequence of SEB at position 226-229 as shown in SEQ ID NO: 1 is Ala Thr Thr Gln or modified SEB mutant 47-C-1 wherein the amino acid sequence of SEB at position 226-229 as shown in SEQ ID NO: 1 is Lys Arg Ile Ile, wherein said mutants produce inhibitory cytokines at higher levels compared to the production of inflammatory cytokines as compared to wild type SEB and wherein said modified SEB mutants are used for treating rheumatoid arthritis but not

enabled for the use of other modified SEB mutants for use as a prophylactic or remedy or treatment for any immunopathy.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

20. Claim 11 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 22 is drawn to a remedy comprising the modified SEB mutant N23Y or 47C7 or 4C1 wherein said mutants have reduced binding to an anti-SEB antibody and wherein said mutants produce inhibitory cytokines at higher levels compared to the production of inflammatory cytokines as compared to wild type SEB for treatment of rheumatoid arthritis.

- Claims 11 and 22 are indefinite because the claims recite laboratory designations "47C7 or 4C1" which do not sufficiently identify the structure of modified SEB mutants assigned these laboratory designations. The specification does not provide a definition for "47C7 or 4C1" and these laboratory designations are not art recognized and laboratory designations are subject to change.
- "N23Y" is referencing a particular amino acid substitution i.e. asparagine at position 23 substituted with tyrosine. However, the claims do not disclose the amino acid sequence in which the substitution is made, thus rendering the claim vague and indefinite.

- Claim 11 recites the limitation "said form" in line 2. There is insufficient antecedent basis for this limitation in the claim because claim 22 from which claim 11 depends does not recite "form".

## *Status of Claims*

Claims 1-9, 11-17 and 21-22 are rejected. Claim 21 is objected to. Claim 23 is withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

No claims allowed.

## *Conclusion*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to OLUWATOSIN OGUNBIYI whose telephone number is 571-272-9939. The examiner can normally be reached on M-F 8:30 am- 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Oluwatosin Ogunbiyi/

Examiner, Art Unit 1645